# Emergence of Drug Resistance during an Influenza Epidemic: Insights from a Mathematical Model

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**A model was developed for the emergence of drug-resistant influenza viruses during a closed population influenza epidemic that occurs in a single wave. The model was used to consider several treatment and chemoprophylaxis strategies and to determine their effects on the spread of the infection. The model predicts frequent emergence and transmission of drug-resistant viruses with certain treatment scenarios. According to the model, chemoprophylaxis of susceptible persons (without treatment of those who are symptomatic) may be the best way to reduce the force of an epidemic and to keep development of drug resistance low. The model predictions indicate that the relative transmissibility of resistant variants compared with wild type virus and the choice of the treatment or chemoprophylaxis strategy can be decisive for the spread of drug-resistant viruses, a feature that may be crucial in a pandemic.**

Antiviral treatment with amantadine and rimantadine has been associated with the emergence of drug-resistant influenza A viruses [1–3]. Such variants are fully resistant to the selective antiviral effects of clinically achievable drug concentrations [4]. Furthermore, in animal models of influenza, the prophylactic activity of amantadine and rimantadine is completely lost when animals are exposed to resistant virus. Drug-treated persons infected with influenza may shed resistant viruses within 2–5 days after starting treatment [1, 3]. The impact of the emergence of drug-resistant viruses and the likelihood of transmission of drug-resistant virus isolates are incompletely defined, although transmission of such variants has been associated with failures of drug prophylaxis in household settings and nursing homes [1–3, 5]. However, in most circumstances, the benefits of drug prophylaxis and therapy appear to outweigh the risks of drug resistance emergence [4].

The epidemiologic significance of the emergence of drug-resistant viruses needs to be addressed before recommendations can be made for large-scale drug administration during a major outbreak or pandemic [6–8]. Strategies need to be determined for drug administration that would keep emergence of drug-resistant viruses at reasonably low levels and minimize the deleterious effects of viral variants. If possible, such strategies should allow prevention of illness and treatment of symptomatic patients to take maximal advantage of the proven prophylactic and therapeutic activities of amantadine and rimantadine. We sought to determine if drug prophylaxis or treatment with amantadine or rimantadine would be an effective intervention method during an influenza epidemic (or pandemic) in a closed population, given the potential rapid emergence and spread of drug-resistant influenza viruses. To address this question, we developed a new mathematical model that describes the effects of drug resistance on the transmission dynamics of an influenza outbreak in a closed population. We also evaluated several drug administration strategies with respect to the degree to which drug treatment or chemoprophylaxis affects the emergence of drug resistance.

## Methods

### Modeling an Outbreak

Several studies have used mathematical models to describe the transmission dynamics of influenza within a susceptible population during an epidemic [9–12]. Although some of those studies addressed the issues of efficacy and optimization of immunization programs, to our knowledge no study has used mathematical modeling to investigate the application of antiviral therapy as a strategy to control influenza epidemics. Mathematical approaches have been used to describe the interference of two influenza virus isolates [12, 13] but not in the context of antiviral therapy. Mathematical models describing the emergence of drug resistance have been applied to other infectious diseases, such as tuberculosis [14].

Strategies for administering antiviral therapy during an influenza epidemic are studied in this paper by using a susceptible-infective-removed (SIR) model in which the total population remains constant and is homogeneously mixed. The assumption of a constant population is reasonable if the infection spreads quickly through the population, as occurs during an influenza epidemic. Further, we assumed that deaths and the time between exposure and beginning of infectiousness were negligible and we ignored high-risk

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groups. To demonstrate the performance characteristics of the model, we first fit data from a previous influenza outbreak that occurred in a single wave in a semiclosed population [15].

The best example of modeling of an influenza epidemic in a closed population is that seen in a school, hospital, or nursing home, where susceptible persons can be assumed to represent an ''idealized'' closed small population. For that purpose, we used data from an influenza A epidemic that occurred from 15 January to 15 February 1978 in a boarding school [15]. We modeled the influenza epidemic with a simple but conceptually new SIR model that, in contrast to the classic SIR approach, included drug resistance and distinguished between two classes of infected and therefore infectious persons: those who were asymptomatic (subclinical infections) and those who developed clinical symptoms (illness).

The reason for this distinction between classes of infected persons was that studies of the effects of amantadine prophylaxis on influenza infections [16–20] indicate that subclinical infections account for about one-third of infections. Since not every infection leads to illness and chemoprophylaxis raises the probability of having a subclinical infection [16–20], therapy or chemoprophylaxis may cause a redistribution among groups of infected persons. In addition, there is a substantial but poorly quantitated difference in transmissibility between transmission from asymptomatic infected to susceptible persons and transmission from symptomatic infected to susceptible persons. An infected person with clinical illness sheds more virus than does one with subclinical infection and also has illness manifestations (e.g., coughing, rhinorrhea) that contribute to the generation of infectious aerosols. However, infected persons with clinical symptoms may show reduced virus transmissibility if they are sufficiently ill to be confined to bed. Thus, the magnitude of differences between the two transmission rates depends on factors such as age, severity of illness, social behavior, and design of living quarters (e.g., common rooms, shared bedrooms).

As with the standard SIR model, we also considered a class of uninfected susceptible subjects and a class of infected persons who recover from subclinical or clinical infections during the epidemic. Transmission of infection results from contacts of the susceptible population with asymptomatic or symptomatic infected persons. Infection of a susceptible person initially leads to subclinical infection (incubation period). Subclinically infected persons either progress to symptomatic infection and then recover or recover without developing clinical symptoms. Transition from the asymptomatic infected stage to the clinically infected stage occurs when a person does not recover before developing clinical illness. All infected persons, with or without symptoms, eventually recover from infection (see Appendix).

We assumed that the epidemic starts in a closed population of susceptible persons with the introduction of a few infected persons with clinical symptoms. Although the epidemic could have started by the introduction of individuals with subclinical infection, they are not easily detectable and ignoring them has little effect on the model.

### Modeling Effects of Drug Administration

Our model is more complex than the standard SIR model, because we consider the effects of drug given either prophylactically (i.e., before infection) or as treatment (i.e., after infection) as well as the generation of drug-resistant virus variants. Thus, the model depicted in figure 1 (see Appendix) considers the following populations (table 1): susceptible persons *(S),* susceptible persons taking drug prophylactically *($S_{pr}$)*, infected untreated *(I)* persons, infected untreated persons who develop clinical symptoms *($I_s$)*, infected untreated asymptomatic persons who shed drug-resistant virus *($I_r$)*, infected untreated persons with clinical symptoms who shed drug-resistant virus *($I_{s,r}$)*, infected treated *($I_{tr}$)* persons, infected treated persons who develop clinical symptoms *($I_{s,tr}$)*, infected treated asymptomatic persons who shed drug-resistant virus *($I_{r,tr}$)*, and infected treated persons with clinical symptoms who shed drug-resistant virus *($I_{s,r,tr}$)*.

In studies of influenza A virus isolates recovered from untreated patients, $<1\%$ of the isolates have been drug-resistant [21]. Although such viruses might represent naturally resistant variants, we assumed that resistant influenza variants are not present at the time the epidemic is recognized. The existence of naturally resistant variants can be easily included in the model by using a positive value for the initial condition of the $I_r$ group.

Identification of the epidemic occurs when $\sim 1\%–5\%$ of the population has been infected. Drug-resistant viruses emerge rapidly after the beginning of treatment (2–5 days) [1, 3]. Thus, we modeled the epidemic as a continuous process starting when 5% of the population is infected and illness is detected. We also assumed that treatment or chemoprophylaxis can begin at this time.

Transmission of infection occurs with a rate $\beta$ and results from contacts of susceptible persons with infected individuals. Transition from the asymptomatic infected to the symptomatic infected stage occurs with a rate $\delta$. Infected persons recover and become immune with a rate $\gamma$ (infectivity period $1/\gamma$). The rate of development of drug resistance is $\kappa$. Finally, the rate at which treatment or chemoprophylaxis is given is denoted as $\theta$. The Appendix gives the population dynamics. Estimates of various model parameters are shown in table 2. In the full model, the parameters $\beta$, $\gamma$, $\delta$, $\kappa$ are given subscripts that denote distinctions among subpopulations (tables 1, 2).

*Transmission.* The transmission rate to a susceptible from an infected untreated person who develops symptoms *($I_s$)* is presumed to be much higher than that to a susceptible from an $I$ person. Susceptible persons are assumed to become infected by $I$ and $I_s$ persons with a higher rate than by $I_r$ and $I_{s,r}$ individuals, because resistant virus is likely to have a lower transmission probability than wild type virus, as suggested by the low prevalence of drug-resistant virus in the absence of selection by drug therapy [21]. However, in persons who shed drug-resistant virus, we assumed that drug treatment does not prolong or reduce viral replication compared with no treatment.

Drug treatment reduces disease severity and the probability of transmitting wild type virus. We assumed that the reduction of transmissibility and therefore the risk of infection when a susceptible person encounters an $I_{tr}$ or $I_{s,tr}$ is about one-third that of an encounter with an $I$ or $I_s$ person (in an epidemic or a pandemic). Our estimate was based on the antiviral effects of drug treatment in symptomatic adults [22] and in reduced secondary cases in household contacts when ill-index cases are given drug treatment [23]. These estimates are valid for an epidemic in which variable degrees of prior immunity exist.

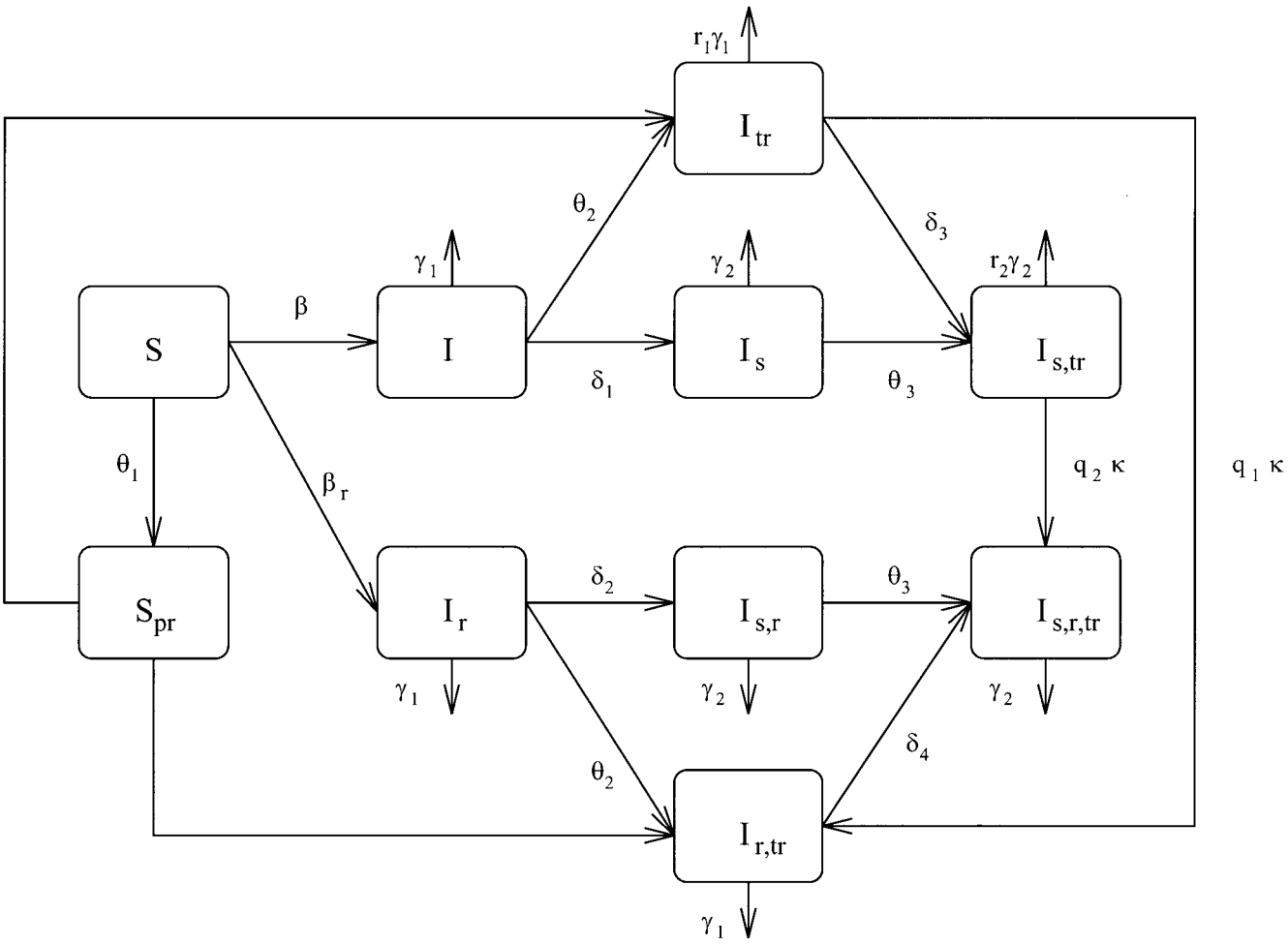


**Figure 1.** Schematic presentation of model populations during treatment. Susceptible *(S)* persons become infected and shed wild type *(I)* or drug-resistant virus *($I_r$)* at rate $\beta$ or $\beta_r$, respectively. Susceptible persons receiving chemoprophylaxis *($S_{pr}$)* at rate $\theta_1$ or instantaneously become infected treated persons who shed drug-sensitive *($I_{tr}$)* or drug-resistant virus *($I_{r,tr}$)*. Asymptomatic infected persons from both groups develop clinical symptoms at rates $\delta_1$ and $\delta_2$, respectively. Treatment is at rate $\theta_2$. Subclinically infected persons, whether shedding drug-sensitive *($I_{tr}$)* or drug-resistant virus *($I_{r,tr}$)*, who receive treatment can become symptomatic at rates $\delta_3$ and $\delta_4$ and continue receiving treatment at rate $\theta_3$ as do symptomatic infected persons *($I_s$, $I_{s,r}$)*. During treatment, asymptomatic infected treated *($I_{s,tr}$)* and symptomatic infected treated persons *($I_{tr}$)* develop drug resistance at rates $q_1\kappa$ and $q_2\kappa$, respectively, where $q_1$ and $q_2$ correspond to likelihood of developing drug resistance ($0 \leqslant q_1, q_2 \leqslant 1$). Then they become symptomatic infected treated persons *($I_{s,r,tr}$)* and asymptomatic infected treated persons *($I_{r,tr}$)*. All infected persons recover at rates $\gamma_1$, $\gamma_2$ (asymptomatic, symptomatic) and $r_1\gamma_1$, $r_2\gamma_2$ (if they are treated) and become immune.

Once drug resistance develops, treatment has little effect. Therefore, we assumed there would be no difference in transmission for contacts of susceptible and infected persons with clinical symptoms shedding resistant virus whether treated *($I_{s,r,tr}$)* or not *($I_{s,r}$)*. These assumptions are based on direct observations in avian influenza [24]. For calculation purposes, we assumed that the transmission probability of drug-resistant viruses is either equal to or, following the observation that de novo infection with drug-resistant virus is very uncommon, 5-fold lower than that of wild type virus.

Chemoprophylaxis is assumed to reduce the susceptibility of contacts [15–20]. The estimates of transmission efficiencies are derived from studies during influenza outbreaks during which treatment and emergence of drug-resistant strains were observed [1–4]. Even though the prophylactic efficacy of amantadine against infection varies from 19% to 52% in pandemics [16–20], most studies have been of populations that were naturally infected with related viruses or immunized before the epidemic. Under those circumstances, the prophylactic efficacy for preventing infection and illness is higher. Consequently, we assumed that an $S_{pr}$ person who encounters an *I*, $I_s$, $I_{tr}$, or $I_{s,tr}$ person is better protected (by $\geqslant$33%) than shown by results derived from chemoprophylaxis during pandemics.

The transmission rate of *I* or $I_s$ subjects to an $S_{pr}$ individual is about two-thirds of the corresponding rate to a susceptible person who does not take chemoprophylaxis. This assumption is based on results of amantadine prophylaxis studies during pandemic influenza [16–20]. The corresponding value for an epidemic due to some degree of prior immunity is assumed to be lower (one-third of the rate for a susceptible person who does not take chemoprophylaxis). The same type of assumption applies for $I_{tr}$ or $I_{s,tr}$ sub-

**Table 1.** Populations considered in the model.

| Symbol | Definition |
|---|---|
| $S$ | Susceptible |
| $S_{pr}$ | Susceptible, taking drug prophylactically |
| $I$ | Infected untreated |
| $I_s$ | Infected untreated, developing clinical symptoms |
| $I_r$ | Infected untreated asymptomatic, shedding resistant virus |
| $I_{s,r}$ | Infected untreated, with clinical symptoms shedding resistant virus |
| $I_{tr}$ | Infected treated |
| $I_{s,tr}$ | Infected treated, developing clinical symptoms |
| $I_{r,tr}$ | Infected treated asymptomatic, shedding resistant virus |
| $I_{s,r,tr}$ | Infected treated, with clinical symptoms shedding resistant virus |

jects who have contact with $S_{pr}$ individuals. The probability that an $I_{tr}$ or an $I_{s,tr}$ person can infect an $S_{pr}$ is assumed to be very small ($\sim$10% vs. the relative infectivity of wild type virus without drug intervention for an epidemic). In an epidemic, the prophylactic efficacy for preventing infection is estimated at 66%–79% and for preventing illness at 85%–91% [25]. In a pandemic, the prophylactic efficacy for preventing infection is estimated at $\sim$33% and $\sim$65% for preventing illness [16–19, 26]. $S_{pr}$ individuals who encounter $I_r$, $I_{s,r}$, $I_{r,tr}$, or $I_{s,r,tr}$ persons are assumed to be unprotected and to have the same transmission rates as their counterparts that do not take chemoprophylaxis.

*Recovery.* The recovery rate (i.e., loss of infectivity) of infected persons appears to be the same for illness due to wild type and drug-resistant virus [1, 4, 27]. Further, we assumed that drug treatment does not enhance recovery of persons infected with resistant virus. In subjects with clinical symptoms, these rates may be slightly different, since infected persons who shed drug-resistant virus (specifically, treated children) may have a somewhat longer infectivity period [27, 28]. Infected persons who have been treated are expected to recover faster.

Persons with clinical symptoms have a slower recovery than asymptomatic infected persons. This assumption does not consider the fact that infected persons with clinical symptoms are to some degree isolated because they tend to avoid contact with susceptible persons or that susceptible persons may be more careful in their behavior when they are near symptomatic persons. Thus, one could argue that it is more likely that their average period of infectivity (removal from the population that transmits the disease) is shorter or almost the same as that of untreated infected persons. However, this is probably outweighed by the likelihood of greater infectivity due to higher virus loads in symptomatic persons. This assumption is reinforced by the documentation of numerous closed population outbreaks. In a pandemic, recovery is likely to last longer than in an epidemic.

*Progression to the symptomatic stage.* The rates at which $I$, $I_r$, $I_{tr}$ and $I_{r,tr}$ persons develop clinical symptoms are assumed to relate to each other such that treatment slows the appearance of clinical symptoms (e.g., $I_{tr}$ subjects become $I_{s,tr}$ at a much lower rate than $I$ become $I_s$). In untreated persons infected with wild type or resistant viruses and in treated persons who shed resistant virus, the development of symptoms is assumed to occur at the same rate (see table 2).

*Development of drug resistance.* Because drug-resistant variants of influenza occur at very low levels in untreated populations, we ignored the spontaneous generation of drug-resistant variants in untreated persons during the course of a single outbreak. However, following treatment, resistance develops in up to 30% of treated persons [1, 4, 28]. Although these data are limited, in the absence of clinical symptoms, we assumed there would be less viral replication and less of a chance of resistance developing (see table 2). Drug resistance can result from failure of drug treatment. In our model, which links two epidemics (one drug-sensitive and one drug-resistant), failure of drug treatment causes acquired resistance to arise directly within infected persons and to arise indirectly from contact between susceptible and infected persons shedding resistant virus.

### Drug Interventions

Drug administration strategies can be subdivided into treatment of infected persons, chemoprophylaxis of susceptible persons, or both. Further, treatment or chemoprophylaxis can be administered at some average rate during the epidemic. A sufficient number of infected persons must be evident to justify introduction of chemoprophylaxis at a specific rate. If not, one can modify the rate $\theta$ so that it is a function of the available infected population [$\theta(I_s)$]. Chemoprophylaxis can be also administered instantaneously at a certain time point, such as in small populations in schools, nursing homes, or hospitals.

Drug administration strategies are modeled by removal rates from one class to another. Susceptible persons can receive chemoprophylaxis at some daily rate that may be time-dependent or a function of the number of infected persons (see Appendix). After treatment, infected persons who shed drug-resistant virus *($I_r$)* or not *($I$)* are reclassified with infected treated individuals (with some rate). Obviously, treatment of a person in the group of asymptomatic infected persons is possible only if their subclinical infective status is detected or if chemoprophylaxis is given. $I_s$ and $I_{s,r}$ persons are also treated at a rate. Although $I_{s,r}$ individuals will probably not respond to treatment, they receive treatment because they are not recognized prospectively as shedding resistant virus.

## Results

### Simple Epidemic Model

The basic SIR model shown in equations A1–A3 (Appendix) illustrates a single wave of an influenza epidemic in a closed population without deaths of those infected. This model is based on a 30-day epidemic in a boarding school with 578 boys [15]. During the epidemic, 166 boys (28.7% of all students) developed influenza illness. The average length of fever or other symptoms was 4 days. The number of subclinical infections was unknown. On day 7 of the epidemic, 31 non-ill boys (5.4% of all students) received amantadine prophylaxis. No investigation was done of possible development of drug-resistant influenza isolates.

Because the boys had been immunized with an influenza vaccine antigenically different from the epidemic virus, it failed to prevent the epidemic [15]. Since our intention was to develop models useful in pandemic situations, we did not include in

**Table 2.** Parameter values for epidemic (epi) and pandemic (pan) used in the model.

| Parameters | | Standard values |
|---|---|---|
| $\beta_1$, $\beta_{1,r}$ | Transmission rate between $I$ and $S$ that is sufficiently close to allow transmission of wild type/drug-resistant virus and cause subclinical infection | $\beta_1 = \beta_{1,r} = 6 \times 10^{-4}$/day or $\beta_{1,r} = \beta_1/5 = 1.2 \times 10^{-4}$/day |
| $\beta_2$, $\beta_{2,r}$ | Transmission rate between $I_s$ and $S$ that is sufficiently close to allow transmission of wild type/drug-resistant virus and cause subclinical infection | $\beta_2 = \beta_{2,r} = 6 \times 10^{-3}$/day or $\beta_{2,r} = \beta_2/5 = 1.2 \times 10^{-3}$/day |
| $p_i$ | Relative infectivity of wild type virus during chemoprophylaxis/treatment compared with that of wild type virus without drug intervention for contacts between | |
| | $I_{tr}$ or $I_{s,tr}$ and $S$; $p_1$, $p_2$ ($p_1 = p_2$ epi/pan) | 0.67 epi/pan [22, 23] |
| | $I$ or $I_s$ and $S_{pr}$; $p_3$, $p_4$ ($p_3 = p_4$ epi/pan) | 0.33 epi; 0.67 pan [16–20] |
| | $I_{tr}$ or $I_{s,tr}$ and $S_{pr}$; $p_5$, $p_6$ ($p_5 = p_6$ epi) | 0.10 epi [25]; 0.35, 0.67 pan [16–19, 26] |
| $\delta_j$ | Transition rate at which $I$ becomes $I_s$ ($\delta_1$), $I_r$ becomes $I_{s,r}$ ($\delta_2$), $I_{r,tr}$ becomes $I_{s,r,tr}$ ($\delta_4$), ($\delta_1 = \delta_2 = \delta_4$) | 0.5/day |
| | $I_{tr}$ becomes $I_{s,tr}$ ($\delta_3$) | 0.10/day epi; 0.17 pan |
| $\theta_l$ | Chemoprophylaxis/treatment rate of: | |
| | $S$; ($\theta_1$); $I$ and $I_r$; ($\theta_2$), | 0.0/day |
| | and $I_s$ and $I_{s,r}$; ($\theta_3$) | 0.70/day |
| $\gamma_1$, $\gamma_2$ | Recovery rate from subclinical infection ($\gamma_1$) or | 0.50/day |
| | infection with clinical symptoms ($\gamma_2$) | 0.25/day [15] |
| $r_1$, $r_2$ | Relative recovery of $I_{tr}$; ($r_1$) (compared with that of $I$); | 2.0 epi; 1.60 pan |
| | $r_2$ relative recovery of $I_{s,tr}$ infection (compared with that of $I_s$) | 1.33 epi; 1.05 pan |
| $\kappa$ | Rate of drug resistance development during treatment of $I_{s,tr}$ that becomes $I_{s,r,tr}$ | 0.25/day [1, 3] |
| $q_1$, $q_2$ | Probability of emergence of acquired drug resistance (due to treatment failure) | |
| | from $I_{tr}$ that becomes $I_{r,tr}$; ($q_1$) or | 0.02 |
| | from $I_{s,tr}$ that becomes $I_{s,r,tr}$; ($q_2$) | 0.20 [1, 4, 28] |

NOTE. $i = 1, \ldots, 6$, $j = 1, \ldots, 4$, $l = 1, 2, 3$. Population variables as in table 1.

our model the possible effect of immunization. Thus, to examine this outbreak, we made some modifications. The number of infected persons in influenza epidemics who develop illness varies widely; there is also a variable fraction of immune (nonsusceptible) persons in a population. We assumed that ~220 (38%) of the 578 boys were totally immune to the influenza virus and therefore not affected during the epidemic. The remaining 358 boys formed our pool of susceptible persons. This number of immune persons is in line with levels of immunity observed in another influenza outbreak at the same school. Amantadine was used in both outbreaks [29]. This number also gives the best fit for our data and lies within the estimates of possible immune persons within a population.

To fit the data, we assumed that an average of 50% of infected persons become sick with clinical symptoms; the rest are subclinically infected. The ratio between the transmission rates of subclinically infected and clinically infected was assumed to be 1:10. We fit the data assuming that chemoprophylaxis was given to 31 boys starting at day 7. According to the data, 24 boys (4.2% of all students) showed clinical symptoms that day. The model predicted that another 10 boys (1.7% of the total population) had already been infected and had recovered between the first case reported and day 7. Figure 2 shows the close agreement between our model and data from the outbreak.

### Epidemic with Treatment

To model the effects of drug administration in the typical epidemic described in figure 2, we introduced treatment at day 7, the time when ~5% of the population has been symptomatically infected, as in the boarding school outbreak [15], and followed the epidemic for 30 days. We compared the outcomes of those infected who showed clinical symptoms with the typical epidemic described above (but without any intervention). The followed three treatment and chemoprophylaxis strategies were

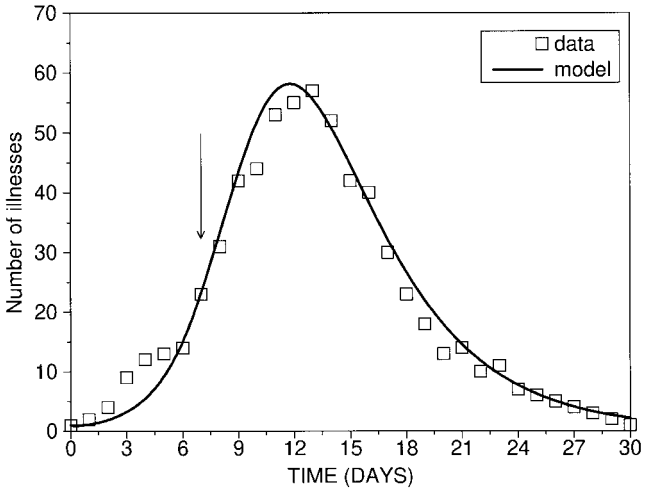


**Figure 2.** Progress of 30-day influenza outbreak in boarding school. Fit of symptomatic infected persons (illnesses). Parameter values: $\beta_1 = 6 \times 10^{-4}$/day, $\beta_2 = 6 \times 10^{-3}$/day, $\delta_1 = 0.50$/day, $\gamma_1 = 0.50$/day, and $\gamma_2 = 0.25$/day. Arrow: Time when chemoprophylaxis was initiated.

**Table 3.** Outcomes after a 30-day epidemic as predicted by the model.

| Strategy/parameter | Without drug intervention | With drug intervention | |
|---|---|---|---|
| | | $\beta = \beta_r$ | $\beta = 5\beta_r$ |
| 1: Treatment of ill infected persons | | | |
| $S$ | 4 | 15 | 23 |
| $S_{pr}$ | — | — | — |
| $I_{stot}$ | 177 | 172 | 167 |
| $I_{srtot}$ | — | 26 | 17 |
| $I_{tot}$ | 354 | 343 | 335 |
| 2: Prophylaxis | | | |
| $S$ | 4 | — | — |
| $S_{pr}$ | — | 77 | 185 |
| $I_{stot}$ | 177 | 107 | 57 |
| $I_{srtot}$ | — | 52 | 2 |
| $I_{tot}$ | 354 | 281 | 173 |
| 3: Treatment of ill infected persons and prophylaxis | | | |
| $S$ | 4 | — | — |
| $S_{pr}$ | — | 22 | 217 |
| $I_{stot}$ | 177 | 154 | 57 |
| $I_{srtot}$ | — | 106 | 8 |
| $I_{tot}$ | 354 | 336 | 141 |

NOTE. Estimates based on total population of 578: 220 are presumed to be immune, $S$ = remaining susceptible persons, $S_{pr}$ = remaining susceptible persons receiving prophylaxis, $I_{stot}$ = total infected persons who developed clinical symptoms ($I_s + I_{s,tr} + I_{s,r} + I_{s,r,tr}$), $I_{srtot}$ = no. of infected persons shedding resistant virus and who developed symptoms ($I_{s,r} + I_{s,r,tr}$), $I_{tot}$ = total infected individuals, and $\beta$, $\beta_r$ = transmission probability of wild type and resistant virus, respectively. Values were rounded up or down to nearest whole number.

considered: treatment of infected persons with clinical symptoms, chemoprophylaxis of all susceptible persons who were not infected by day 7, and treatment of symptomatic infected persons as in scenario 1 and chemoprophylaxis for all susceptible persons as in scenario 2.

*Strategy 1.* One plausible approach is treatment only of infected persons with clinical symptoms. We chose a per capita treatment rate of 0.70/day for $I_s$ and $I_{s,r}$ subjects, which implies that the time to treat half the population is 1 day. With this treatment rate, there is a modest damping of the epidemic. The total number of infected persons with symptoms is ~50% of all infected persons (table 3). Figure 3A shows that after the introduction of treatment the fraction of $I_{s,tr}$ individuals (dotted line) continues to increase for ~4 days and then declines. This would reduce the epidemic further if no resistance developed. The model, however, predicts the initiation of a smaller new wave of infections caused by drug-resistant variants that emerge from the treatment of those infected (figure 3A, dashed line). Because the number of infected persons shedding drug-resistant virus is relatively small, the emergence of drug-resistant virus does not prolong the epidemic.

The cumulative fraction of infected subjects with clinical symptoms who shed resistant virus after 30 days is 12.5% of all symptomatic individuals (after initiation of therapy). The fraction of ill individuals is 46.6% of the initial susceptible population. Thus, under the assumption of a lower transmission probability of drug-resistant virus compared with wild type virus, the model predicts relatively low numbers of infections with drug-resistant virus. If the transmission probability difference between those shedding wild type and drug-resistant virus was smaller or it was equal, the transmissibility would remain almost as high as before the initiation of treatment for the treated group, and this would cause an even larger second wave of the epidemic (table 3). There is a minor reduction (2.4%) in numbers of infected persons. Therefore, although treatment

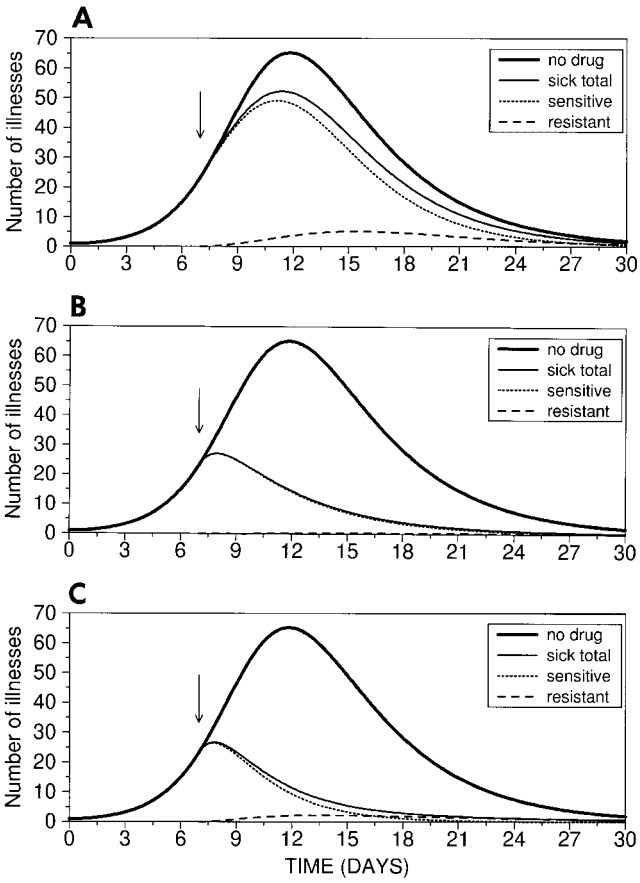


**Figure 3.** Treatment and/or chemoprophylaxis during influenza outbreak introduced after 7 days (arrow) into epidemic compared with epidemic without intervention. Assumption that drug-resistant virus is transmitted with 5-fold lower probability than wild type (drug-sensitive) virus ($\beta_1 = 5\beta_{1,r}$ and $\beta_2 = 5\beta_{2,r}$). **A**, Symptomatic infected persons treated at daily rate. Total ill: $I_s + I_{s,tr} + I_{s,r} + I_{s,r,tr}$; no. of infected persons shedding wild type virus $I_s + I_{s,tr}$ (dotted line); population shedding resistant virus $I_{s,r} + I_{s,r,tr}$ (dashed line). **B**, Introduction of instant chemoprophylaxis (only) at day 7 to all susceptible persons. Representation of populations as in **A**. **C**, Combined strategy of treatment and chemoprophylaxis under assumptions **A** and **B**. Population as in **A**. Parameter values (per day): $\beta_1 = 6 \times 10^{-4}$, $\beta_2 = 6 \times 10^{-3}$, $p_1 = p_2 = 0.67$, $p_3 = p_4 = 0.33$, $p_5 = p_6 = 0.10$, $\gamma_1 = 0.50$, $\gamma_2 = 0.25$, $r_1 = 2.0$, $r_2 = 1.33$, $\delta_1 = \delta_2 = \delta_4 = 0.50$, $\delta_3 = 0.10$, $q_1 = 0.02$, $q_2 = 0.20$, $\kappa = 0.25$, $\theta_1 = \theta_2 = 0.00$, $\theta_3 = 0.70$.

of symptomatic infected persons provides some therapeutic benefit, it leads to drug resistance without significant dampening of the epidemic.

*Strategy 2.* Another simple strategy is to give chemoprophylaxis to all susceptible persons who have not yet been infected, that is, mass chemoprophylaxis for outbreak control. The distribution of the drug is assumed to be instantaneous and chemoprophylaxis is initiated at day 7.

Figure 3B shows that after 1 day the fraction of infected symptomatic persons declines rapidly and, most importantly, the model predicts very little emergence of resistant virus caused by primary infections through chemoprophylaxis failures (figure 3B). The number of infected symptomatic persons after 30 days is significantly lower than under strategy 1 by about two-thirds. The epidemic is predicted to last significantly less than if no chemoprophylaxis was given.

The model predicts a fast and strong damping of the epidemic with a small fraction of cases where infected persons shed drug-resistant virus (figure 3B). The number of symptomatic infected persons declined 1 day after the introduction of chemoprophylaxis, and within 14 days of the initiation of chemoprophylaxis, there were no infected persons. About 71.4% of those given chemoprophylaxis at day 7 remain uninfected at day 30 (table 3). Only 16% of the initially susceptible population become ill. Moreover, the total number of infected persons with clinical symptoms shown to be infected during the 30-day period is only ~32% of the case totals in the original epidemic, and the epidemic passes rapidly. Only 3.5% of all symptomatic infected persons shed resistant virus (7.7% of the symptomatic infected persons) after the introduction of chemoprophylaxis.

These predictions are in line with the finding from mass chemoprophylaxis for nursing home outbreak control (e.g., [30]). If the transmission probability of drug-resistant variants is higher or equal to that of wild type virus, a second epidemic will be caused by the drug-resistant variant, the epidemic will last significantly longer, and a high number of infections with resistant virus will be observed (table 3). However, the predictions shown in figure 3B correlate with data from mass chemoprophylaxis (with or without treatment of ill persons), since outbreaks usually end and the number of clinical prophylaxis failures is very low, even in studies reporting the emergence of resistant variants [2, 3, 5].

Thus, if the transmission probability of drug-resistant variants is lower than that of the wild type virus, chemoprophylaxis would offer high levels of protection and be a very successful prevention strategy.

*Strategy 3.* Our third approach combines chemoprophylaxis with treatment of infected persons and uses the same assumptions as in strategies 1 and 2. Figure 3C shows that the combined treatment gives similar results as strategy 2 (table 3).

For the same reasons as in strategy 1, treatment favors drug resistance, depending on the probability of virus transmission by persons shedding drug-resistant virus compared with that of wild type virus (table 3). Chemoprophylaxis, treatment, or both offer some protection to those in contact with infected persons shedding wild type virus but no protection against resistant virus. This gives an advantage to emergence and faster transmission of resistant virus, which replaces wild type virus among infected persons. Also, in this scenario, the total number of infected subjects is significantly less (40% of total infected persons) than in the original epidemic and there is substantial beneficial effect with respect to the total epidemic, although not when the transmissibility of resistant virus is comparable to that of wild type (table 3). The fraction of sick infected persons who shed resistant virus among all ill individuals during the 30-day epidemic is low, ~14%. These predictions are in line with data from nursing home outbreak control studies that used mass chemoprophylaxis combined with treatment [2, 3, 5].

Figure 3C shows that the combined protective effects of chemoprophylaxis and treatment cause a sharp decline in the number of new cases of illness. Because there are few sick individuals, the emergence of drug resistance also remains relatively low, although the number of infected persons is higher than with chemoprophylaxis. The duration of the epidemic is much shorter than the original epidemic without any intervention. In contrast, if the transmission probability of resistant virus is equal to that of wild type virus, the model predicts large numbers of illnesses due to resistant virus (table 3).

Combined strategies can only be successful if the fraction of treatment and chemoprophylaxis failures remains small or if the protective effect of chemoprophylaxis and the reduction of susceptibility during treatment are sufficiently high. The transmission probability of drug-resistant virus must be sufficiently low to avoid a second epidemic wave caused by the drug-resistant variant.

### Pandemic Situation

To investigate the effect of an antigenically shifted influenza isolate introduced in a small closed population and for which the population lacks significant protective immunity, we simulated that scenario. A pandemic in a closed population differs from that of an epidemic in such a population in three important respects: the reduction of susceptibility and infectivity caused by drug administration, the lack of immunity expressed in the initial number of susceptible persons, and a prolonged infectivity period. During a pandemic, in contrast to an epidemic, there may be no population immunity. For our example, the initial population is increased to all 578 boys in the boarding school. The model predicts the same number of infections as in the epidemic (24 persons) after 4 days. Another 4 persons are predicted to have recovered within this time. Thus, to keep results somewhat comparable to an epidemic, we started drug administration after 4 days when ~4.2% of all students would be infected.

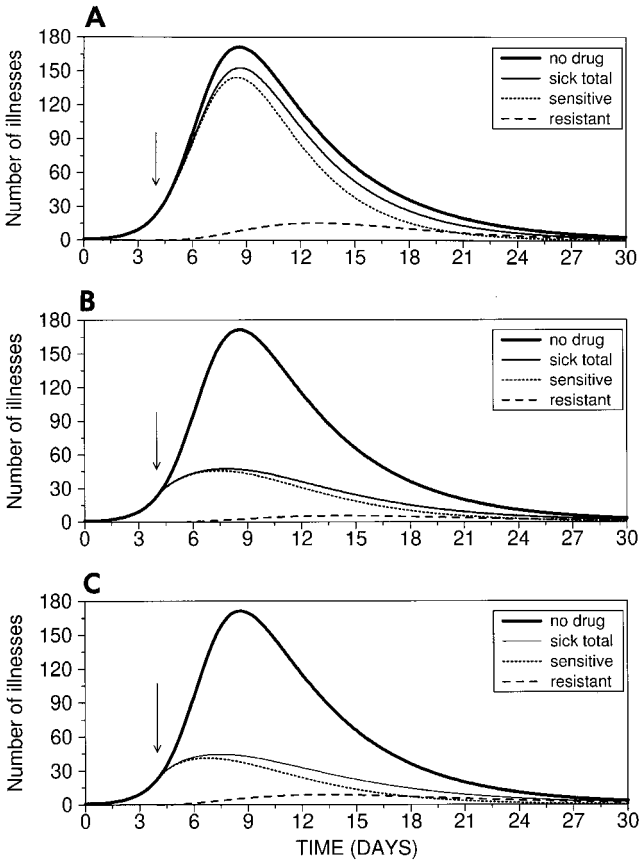


**Figure 4.** Pandemic (no immunity within initial susceptible population) for same strategies and populations as in figure 3. Parameter values (per day): $\beta_1 = 6 \times 10^{-4} = 5\beta_{1,r}$, $\beta_2 = 6 \times 10^{-3} = 5\beta_{2,r}$, $p_1 = p_2 = p_3 = p_4 = p_6 = 0.67$, $p_5 = 0.35$, $\gamma_1 = 0.50$, $\gamma_2 = 0.25$, $r_1 = 1.6$, $r_2 = 1.05$, $\delta_1 = \delta_2 = \delta_4 = 0.50$, $\delta_3 = 0.17$, $q_1 = 0.02$, $q_2 = 0.2$, $\kappa = 0.25$, $\theta_1 = \theta_2 = 0.00$, $\theta_3 = 0.70$.

The protective effect of drug administration was assumed to be somewhat less than in the epidemic (table 2). Chemoprophylaxis studies conducted during epidemics and pandemics with different subtypes of influenza A viruses have found different levels of protective efficacy of amantadine prophylaxis [16–20, 31, 32].

Figure 4 shows results of the three strategies. The striking feature of the pandemic model is the high number of infected persons: Within 30 days, all susceptible persons would become at least subclinically infected and 55.5% of these will have clinical symptoms (table 4). The differences between the epidemic and pandemic models included a larger susceptible population, worse drug efficacy, and lower recovery rates in the pandemic (~20%).

In a pandemic, the effects of the three strategies are similar to those predicted for an epidemic (figure 4; table 4). Chemoprophylaxis represents the most beneficial strategy, followed by the combined strategy of treatment and chemoprophylaxis. Treatment and chemoprophylaxis combined would produce almost the same number of symptomatic infected persons as would administration of chemoprophylaxis alone. However, chemoprophylaxis alone would produce fewer infections with drug-resistant virus.

Chemoprophylaxis or a combination of treatment and chemoprophylaxis during a pandemic would reduce symptomatic cases by ~41%. Drug resistance with either strategy would be 13.5%–22.3% of total symptomatic infections. Again, these results assume that the transmission probability of drug-resistant strains is lower than that of wild type virus. If this is not the case, the number of infections with drug-resistant virus would be much higher (table 4).

## Discussion

We investigated whether drug chemoprophylaxis and/or treatment with amantadine or rimantadine can be an effective intervention during an influenza epidemic or pandemic in a closed population, given the potential rapid emergence and spread of drug-resistant influenza isolates. To address this question, we developed a new mathematical model of influenza spread that incorporates several possible strategies for drug administration. The results of the model suggest the following:

First, treatment only of those who develop clinical symptoms would be associated with no important effect in slowing the

**Table 4.** Outcomes after a 30-day pandemic as predicted by the model.

| Strategy/parameter | Without drug intervention | With drug intervention | |
|---|---|---|---|
| | | $\beta = \beta_r$ | $\beta = 5\beta_r$ |
| 1: Treatment of ill infected persons | | | |
| $S$ | 0 | 0 | 1 |
| $S_{pr}$ | — | — | — |
| $I_{stot}$ | 321 | 321 | 320 |
| $I_{srtot}$ | — | 48 | 41 |
| $I_{tot}$ | 578 | 578 | 577 |
| 2: Prophylaxis | | | |
| $S$ | 0 | — | — |
| $S_{pr}$ | — | 11 | 57 |
| $I_{stot}$ | 321 | 173 | 133 |
| $I_{srtot}$ | — | 65 | 18 |
| $I_{tot}$ | 578 | 567 | 521 |
| 3: Treatment of ill infected persons and prophylaxis | | | |
| $S$ | 0 | — | — |
| $S_{pr}$ | — | 5 | 75 |
| $I_{stot}$ | 321 | 196 | 134 |
| $I_{srtot}$ | — | 101 | 30 |
| $I_{tot}$ | 578 | 573 | 503 |

NOTE. Estimates based on total susceptible population of 578. $S$ = remaining susceptible persons, $S_{pr}$ = remaining susceptible persons receiving prophylaxis, $I_{stot}$ = total infected persons who developed clinical symptoms ($I_s + I_{s,tr} + I_{s,r} + I_{s,r,tr}$), $I_{srtot}$ = number of infected persons who shed resistant virus and developed symptoms ($I_{s,r} + I_{s,r,tr}$), $I_{tot}$ = total infected subjects, $\beta$, $\beta_r$ = transmission probability of wild type and resistant virus, respectively. Values were rounded up or down to nearest whole number.

epidemic and with a variable risk of developing drug resistance. The degree to which drug resistance can emerge depends on the probability with which individuals undergoing drug therapy shed resistant virus and the transmissibility of resistant virus relative to wild type virus. This conclusion is strongly linked to our basic assumptions that symptomatic infected persons can transmit influenza very rapidly and that drug efficacy for treatment is only partial with respect to clinical and antiviral effects. Equal transmission probability of drug-resistant and wild type virus significantly favors the emergence of drug-resistant virus. Partial drug efficacy also contributes to this phenomenon, since when there is only a small reduction in transmission, a relatively high level of those who remain infected provides the necessary time for drug-resistant isolates to emerge and be transmitted. Thus, a person once infected sheds resistant virus with a certain probability that may vary from isolate to isolate. This probability and the timing of onset of resistant virus is decisive for transmitting drug-resistant virus.

Second, a strategy of chemoprophylaxis leads to lower levels of infection during the epidemic, although a substantial number of persons remain susceptible to infection. Emergence of drug resistance is predicted to be low. A strong blocking of the epidemic occurs and the epidemic is shorter than without any intervention, making this strategy superior to the previous one. In a pandemic, this approach moderately reduces the number of symptomatic infected persons.

Third, combining treatment of infected symptomatic persons with chemoprophylaxis for susceptible persons has effects that are similar to the second strategy. Intensive treatment and chemoprophylaxis strongly suppress the epidemic with low emergence of drug-resistant virus, but this conclusion depends heavily on the relative transmissibility of resistant and wild type virus. We assumed a 5-fold reduction in relative transmissibility to make the model predictions (table 3) fit the observations in nursing home outbreaks [1–5].

Our results are only applicable to small closed populations such as those found in nursing homes, boarding schools, prisons, and hospitals. If the population size were significantly larger and not closed, such as a city, the model would need to be modified. However, no large-scale studies document drug resistance in populations of the magnitude of those in a city. Such work would be beneficial for large-scale planning efforts involving either chemoprophylaxis or drug treatment of infected persons.

The efficacy of amantadine and rimantadine in several household setting studies using postcontact chemoprophylaxis and treatment of infected persons shows enormous variation (3%–100%) [1, 31, 32]. This variation, which may be related to differences among isolates or in study design, corresponds to transmission of resistant virus and associated failures of drug prophylaxis in household settings [1] where both treatment of ill index cases, particularly young children, and postcontact chemoprophylaxis have been used. In the model, treatment and chemoprophylaxis showed beneficial effects and can be regarded as an alternative to chemoprophylaxis alone in closed populations, although little observational data exist [2, 3, 5].

Most studies of influenza epidemics have been in populations that have had prior exposure to influenza or immunization. This makes quantification of drug efficacy and the drug-dependent development of resistant viruses uncertain. If our first estimates about the efficacy by treatment and chemoprophylaxis based on prior studies are correct, then treatment could be endorsed as a means of reducing epidemic spread for large-scale interventions only with caution because of the emergence of drug resistance.

It must be emphasized that behavioral differences among individuals may significantly influence the relationships that we have assumed between the various rates used in the model. Before adapting a treatment strategy for a population facing an epidemic or pandemic, the specific pattern of the interrelation between transmission and recovery rates of the different infections needs to be determined with some accuracy. The available data are characterized by strong variation, and questions of drug efficacy for different strains, transmissibility differences, and probability of drug resistance emergence are unanswered. Therefore, our results should be regarded with caution. Furthermore, in a pandemic, the large number of susceptible persons and the lower drug efficacies for prevention and treatment tend to increase the extent of drug resistance and transmission.

In summary, if drug administration strongly reduces influenza transmission and protects susceptible persons taking chemoprophylaxis, then our model predicts that chemoprophylaxis can be very beneficial, and emergence of drug resistance can be kept at low levels. Chemoprophylaxis combined with drug treatment of symptomatic infected persons also appears to be positive in dampening an epidemic. On the other hand, drug treatment of symptomatic infected persons benefits this group only and has little effect on the epidemic. The model predictions point out the necessity of obtaining better estimates for drug efficacy. Given that drug administration does not have any effect in infections with drug-resistant influenza isolates [24] and the partial efficacy in treatment of infections with wild type virus, the model suggests that a low probability of drug resistance emergence and transmission can explain the relatively low frequency of drug resistance emergence in closed population outbreaks [2, 3, 5]. Otherwise, enforcement of the development of drug-resistant isolates, which cause secondary epidemics within the original one, is the consequence.

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## Appendix

*Influenza epidemic model.* The variables used in the model to describe the influenza outbreak *(S, I, $I_s$)* are listed in table 1. The system of nonlinear differential equations that gives the model dynamics is shown in equations A1–A3:

$$\frac{dS}{dt} = -(\beta_1 I + \beta_2 I_s)S, \quad \text{(A1)}$$

$$\frac{dI}{dt} = (\beta_1 I + \beta_2 I_s)S - (\delta_1 + \gamma_1)I, \quad \text{(A2)}$$

$$\frac{dI_s}{dt} = \delta_1 I - \gamma_2 I_s, \quad \text{(A3)}$$

with $S(t_0) = S_0$, $I(t_0) = 0$, $I_s(t_0) = I_{s0}$. Since the model does not include death from influenza, all infected persons recover with a rate $\gamma_1$ (from asymptomatic infection) and $\gamma_2$ (from symptomatic infection). Further, the total population size, *N,* is assumed to remain constant. Thus, the fraction of persons who are removed *(R)* can be calculated from $R = N - (S + I + I_s)$. The corresponding parameter values ($\beta_1$, $\beta_2$, $\gamma_1$, $\gamma_2$) are shown in table 2.

*Influenza epidemic model with drug intervention.* The above model is expanded so that it describes drug intervention during an influenza epidemic and includes the populations shown in table 1. The dynamics of those populations are given by the following equations:

$$\frac{dS}{dt} = -(\beta_1 I + \beta_2 I_s + \beta_{1,r} I_r + \beta_{2,r} I_{s,r} + p_1\beta_1 I_{tr} + p_2\beta_2 I_{s,tr} + \beta_{1,r} I_{r,tr} + \beta_{2,r} I_{s,r,tr})S - \theta_1 S, \quad \text{(A4)}$$

$$\frac{dS_{pr}}{dt} = -(p_3\beta_1 I + p_4\beta_2 I_s + \beta_{1,r} I_r + \beta_{2,r} I_{s,r} + p_5\beta_1 I_{tr} + p_6\beta_2 I_{s,tr} + \beta_{1,r} I_{r,tr} + \beta_{2,r} I_{s,r,tr})S_{pr} + \theta_1 S, \quad \text{(A5)}$$

$$\frac{dI}{dt} = (\beta_1 I + p_1\beta_1 I_{tr} + \beta_2 I_s + p_2\beta_2 I_{s,tr})S - (\gamma_1 + \delta_1 + \theta_2)I, \quad \text{(A6)}$$

$$\frac{dI_s}{dt} = \delta_1 I - (\gamma_2 + \theta_3)I_s, \quad \text{(A7)}$$

$$\frac{dI_r}{dt} = (\beta_{1,r}I_r + \beta_{1,r}I_{r,tr} + \beta_{2,r}I_{s,r} + \beta_{2,r}I_{s,r,tr})S + (\beta_{1,r}I_r + \beta_{2,r}I_{s,r})S_{pr} - (\gamma_1 + \delta_2 + \theta_2)I_r, \quad \text{(A8)}$$

$$\frac{dI_{s,r}}{dt} = \delta_2 I_r - (\gamma_2 + \theta_3)I_{s,r}, \quad \text{(A9)}$$

$$\frac{dI_{tr}}{dt} = (p_3\beta_1 I + p_4\beta_2 I_s + p_5\beta_1 I_{tr} + p_6\beta_2 I_{s,tr})S_{pr} - (r_1\gamma_1 + \delta_3 + q_1\kappa)I_{tr} + \theta_2 I, \quad \text{(A10)}$$

$$\frac{dI_{s,tr}}{dt} = \delta_3 I_{tr} - (r_2\gamma_2 + q_2\kappa)I_{s,tr} + \theta_3 I_s, \quad \text{(A11)}$$

$$\frac{dI_{r,tr}}{dt} = (\beta_{1,r}I_{r,tr} + \beta_{2,r}I_{s,r,tr})S_{pr} - (\gamma_1 + \delta_4)I_{r,tr} + q_1\kappa I_{tr} + \theta_2 I_r, \quad \text{(A12)}$$

$$\frac{dI_{s,r,tr}}{dt} = \delta_4 I_{r,tr} - \gamma_2 I_{s,r,tr} + q_2\kappa I_{s,tr} + \theta_3 I_{s,r}, \quad \text{(A13)}$$

with $S(t_1) = S_{0,1}$, $I_s(t_1) = I_{s0,1}$, $I(t_1) = I_{0,1}$, $I_r(t_1) = I_{s,r}(t_1) = I_{tr}(t_1) = I_{s,tr}(t_1) = I_{r,tr}(t_1) = I_{s,r,tr}(t_1) = 0$, and $t_1 > t_0$, where $t_1$ is the time point at which intervention starts.

As stated in the simple model, the fraction of persons who recover and are removed ($R_{tot}$) can be calculated from equation A14.

$$R_{\text{tot}} = N - (S + S_{pr} + I + I_s + I_r + I_{s,r} + I_{tr} + I_{s,tr} + I_{r,tr} + I_{s,r,tr}). \quad \text{(A14)}$$

The parameters and their values included in the model are listed in table 2.